UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

S.M.

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/765,026	01/13/1997	MARTINE BARKATS	ST94051-US	5544

7590 02/25/2004

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315

EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	08/765,026	BARKATS ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,61-75,78,79 and 81-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,61-75,78,79 and 81-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed November 19, 2003.

Claims 47, 61-75, 78, 79 and 81-83 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed May 20, 2003, that is not addressed in this action has been withdrawn.

Applicant's arguments with respect to claims 47, 61-75, 78, 79 and 81-83 have been considered but are moot in view of the new ground(s) of rejection.

Applicant is advised that the examination of the Application has been transferred from the previous Examiner to David A. Lambertson, Ph.D., to whom all further communications should be addressed.

Information Disclosure Statement

The information disclosure statement filed November 19, 2003 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 61-75, 78, 79 and 81-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new rejection that is not necessitated by amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a method of gene therapy. Specifically, the invention claims a method whereby a gene encoding a superoxide dismutase (SOD-1) is used to treat a variety of chronic diseases, such as diabetes, Alzheimer's disease, Parkinson's disease, etc., which have been shown to be associated with the overproduction of highly reactive oxygen species, such as free radicals. The therapeutic gene is expressed in a recombinant replication defective adenovirus. Because the invention claims a method of treatment of these chronic diseases, the method necessarily requires the ability to sustain therapeutic levels of expression of the superoxide dismutase gene. This is because the chronic nature of the diseases requires a sustained expression in order to treat the disease for the length of the patient's affliction therewith.

Scope of the invention. The scope of the invention is very broad, encompassing the ability to treat a large number of chronic diseases.

State of the art and Level of skill in the art. The State of the art indicates that gene therapy, as a whole, is an unpredictable area. This is especially true with regard to the use of adenovirus to sustain the expression of a gene at therapeutic levels.

Verma *et al.* (*Nature* **389**: 239-242, 1997; see entire document; henceforth Verma) states that, "[T]here are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression" (see for example p. 241, center column, first full paragraph). In particular, cells that are infected with recombinant adenovirus expressing a gene of interest are generally only capable of expressing genes for a short period of time, such as 5-10 days (see for example p. 241, left column, second full paragraph). This is generally a result of the immunological response to the adenoviral proteins within the viral vector, to which most humans already have antibodies (see for example p. 241, left column, second and third full paragraphs).

Anderson (*Nature* **392**: 25-30, 1998; see entire document; henceforth Anderson) also discusses many of the pitfalls of gene therapy using adenoviral vectors, indicating how the immune response to the vector often affects the ability of the vector to serve a legitimate therapeutic function (see for example page 28, left column, first and second full paragraphs).

Mountain (*TIBTCH* **18**: 119-128, 2000; see entire document; henceforth Mountain) also discusses the deficiencies associated with using adenoviral vectors (Ad) in a therapeutic capacity. Again, the central theme is that the sustained expression of therapeutic levels of the gene of interest is difficult, if not impossible, to achieve. Mountain specifically states that "Ad vectors are not suitable for the long-term correction of chronic diseases" (see for example page 12, left column, last paragraph), thus indicating a high degree of unpredictability with regard to

the instantly claimed invention of using such vectors to treat chronic diseases such as Alzheimer's or diabetes. This again stems from the propensity of Ad vectors to elicit a strong immune response, causing the formation of antibodies against the virus, and the subsequent abrogation of further gene expression via the adenoviral vector (see for example page 121, right column second full paragraph).

Finally, as it regards gene therapy as a whole, recent reports regarding what was considered the only successful gene therapy technique now show the high degree of unpredictability of treatment. The treatment of SCID by gene therapy has recently been shown to induce the formation of leukemia in some of its patients (Check, E. *Nature* **421**: 305, 2003; see entire document). Thus, this establishes the unpredictability of practicing gene therapy without inducing some alternative condition.

When considering the State of the art, which shows that gene therapy using Adenoviral vectors is highly unpredictable, especially with regard to chronic diseases, the skilled artisan would be forced to turn to the instant specification in order to practice the claimed invention. Specifically, the skilled artisan would look for the ability to express the therapeutic gene, SOD-1, in the sustained manner necessary for treating the indicated chronic diseases (i.e., diabetes, Alzheimer's, etc.), without inducing an immune response abrogating the therapy. This would necessarily require an Ad vector which overcomes the deficiencies of those currently known in the art.

Number of working examples and Guidance provided by applicant. The instant specification does not provide any guidance or working examples to overcome the deficiencies set forth in the State of the art. There is no indication of a manner in which an adenoviral vector

can be used for successive treatments of a condition, wherein the level of expression of the SOD-1 gene is not rapidly decreased to a level that is below therapeutic effectiveness. Rather, the specification merely describes putting the SOD-1 gene into an Ad vector, and prophetically claims its ability to serve as an adequate gene therapy device. There are no working examples of a therapeutic use for the vector, and there is no indication that such a vector has any effect in a model system for any of the diseases it is claimed to treat.

The State of the art, even at post-filing of the application, indicates that this demonstration is insufficient to enable the claimed invention. This is because there is no indication that the vector described in the instant specification has any capacity to overcome the deficiencies of using Ad vectors for gene therapy, as set forth in the State of the art. Thus, when viewing the claimed invention from the perspective of the State of the art and the instant specification, the skilled artisan would have many unanswered questions with regard to using the invention as claimed.

Unpredictability of the art and Amount of experimentation required. In order to practice the instantly claimed invention, the skilled artisan would be forced to practice an incredible amount of undue and unpredictable trial and error experimentation. The State of the Art, even at post-filing to the instant application, indicates that there are no Ad vectors that can adequately sustain the expression of a therapeutic gene in a human. This is because of the elicitation of a strong immune response in the cells upon delivery of the vector, which subsequently results in decreased expression of the therapeutic gene. This is particularly important as it regards the diseases indicated as being treated in the instant claims because these diseases, being chronic in nature, require a long-term method of expressing the therapeutic gene. Thus, in order to practice

the claimed invention, the skilled artisan would need to first develop an Ad viral vector that was capable of expressing a therapeutic gene at sustained levels sufficient to treat a chronic disease. This, in and of itself, would be an invention almost 10 years after the filing of the instant specification, as there is still no indication of such a vector in the post-filing art of 2004. Thus, such an endeavor would be considered an undue and unpredictable (as it is still not clear that such a vector is even possible) amount of empirical experimentation. As a result of the need to establish a vector that could be successfully used in the claimed invention, a method of using such a vector cannot be enabled as of the filing date of the instant specification.

In conclusion, the instantly claimed invention is not enabled because there is no currently known way to sustain the expression of a therapeutic gene in a human, by using an adenoviral vector. In the absence of a teaching of such a vector, the skilled artisan would be unable to use the claimed invention to treat a chronic disease, such as diabetes or Alzheimer's, which necessarily requires that the therapeutic gene be expressed for an extended duration of time.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER